REMARKS

The Present Invention

The present invention is related to mild, enzyme driven methods for removing amine and hydroxide protecting groups.

Amendments to the Claims

Claims 11 - 14 were canceled in response to a restriction requirement. Claims 1 and 9 have been amended to address Section 112 rejections. New claims 21 – 33 have been added. Claims 21 and 31, which have been substituted for original claims 5 and 6, serve to make allowable subject matter objected to in claims 5 and 6, as set forth in the January 6, 2004 Office Action. New Claims 22 – 29 and 32 - 33 have been added to claim subject matter that applicants believe satisfy the statutory requirements for allowance. The new claims and amendments contain matter that may be found in the specification as originally filed, for example, at page 7, line 30 to page 8, line 30, the Examples, and the original claims. Accordingly, no new matter has been added by way of the aforesaid new claims and amendments.

The Pending Claims

Claims 1 - 4, 7 - 10 and 15-33 are now pending in this application. Claims 1 – 4, 7 - 10 and 15-33 relate to enzyme driven methods for removing amine and hydroxide protecting groups.

The Office Action

In the Office Action, the specification was objected to as to containing an incorrect structure.

In the Office Action, the following rejections are set forth:

1. Claims 1, 3-9, 15, 17, and 19 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite;
2. Claims 1, 3 and 7 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated;
3. Claims 1-3, 7 and 9-10 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated;
4. Claims 1 – 4, 7 - 10 and 15-20 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable in view of the prior art; and

5. Claims 5 and 6 are objected to as allegedly being dependent upon a rejected base claim.

Objections as to Incorrect Structure

The specification stands objected to as to containing an incorrect structure on page 6, line 14 in view of the amendments made in applicants' Amendment and Response to Restriction Requirement filed on November 3, 2003. Applicants respectfully submit that the structure in question was amended in the manner suggested by the Examiner in applicants' Amendment and Response to Restriction Requirement filed on November 3, 2003, which is incorporated herein as if set forth at length. See the bottom of page 2 of applicants' Amendment and Response to Restriction Requirement filed on November 3, 2003. In view of the remarks presented above, applicants respectfully request that the objections as to the specification containing an incorrect structure be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1, 3-9, 15, 17, and 19 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Office Action contends that in claims 1 and 9 the phrase "Ar refers to an aromatic or heteroaromatic ring with 5 to 6 ring atoms and one to two heteroatoms selected from O, N or S" is confusing because it is not understood how the aromatic ring could have heteroatoms and not be heteroaromatic.

It is believed that one of ordinary skill in the art would understand that the heteroaromatic ring and not the aromatic ring would contain "one to two heteroatoms selected from O, N or S". However, in order to expedite the prosecution of this application, applicants have amended claims 1 and 9 to overcome the aforementioned rejection. In particular, as suggested by the Examiner, claims 1 and 9 have been amended to clarify that only the heteroaromatic ring contains heteroatoms. Because the Section 112, second paragraph, rejection has been rendered moot by the aforementioned amendments, applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. §102(b)

Claims 1, 3 and 7 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Pohl et al. (J. Am. Chem. Soc. 1997, 119, pp. 6702-6710). Applicants respectfully traverse the rejection and request withdrawal of the Section 102(b) rejection because the cited reference is inapt as Section 102 art, as follows:

The Office Action contends that Pohl et al. shows a method of removing PhAcOZ blocked amines of peptides by the action of penicillin G acylase and that while it is clear the action of the enzyme is to remove the phenylacyl group allowing subsequent decomposition to give the free amine rather than direct cleavage of the urethane linkage, the instant claims merely recite that the action of the enzyme is to release the free amine.

Applicants respectfully submit that, contrary to the Office Action's contention, Pohl et al. does not anticipate the claimed methods in that it fails to disclose a method wherein the protecting group itself and not a portion of the protecting group is removed to recover the amine as required in independent claim 1. Pohl et al.'s method, as indicated in the Office Action on page 3, last paragraph, is a method wherein deprotection of phenylacetoxybenzyloxycarbonyl ("PhAcOZ") blocked amines of peptides occurs through the use of penicillin G acylase as a biocatalyst to cleave the phenylactyl portion of PhAcOZ to provide a functional group, namely *p*-hydroxybenzyl urethane, which undergoes fragmentation resulting in the liberation of a carbamic acid derivative which decarboxylates to give the peptide or peptide conjugate. In contrast, the present invention as hereby claimed in independent claim 1 describes a method for deprotecting an amine protected with a protecting group that does not remove only a portion of the protecting group thus allowing subsequent decomposition to give the free amine. Rather, the method of the present invention requires in independent claim 1 the removal of the protecting group itself to allow recovery of the amine.

In addition, the Pohl et al. reference is inapt as Section 102 art because it fails to disclose a method of deprotecting a hydroxide protected with a protecting group. Pohl et al.'s method is limited to a method of deprotecting PhAcOZ blocked *amines* of peptides. In contrast, the present invention as hereby claimed in independent claim 1 describes a method for deprotecting a moiety that is not limited to PhAcOZ blocked *amines* of peptides. Rather, the method of the present invention can be used to deprotect a hydroxide protected with a protecting group.

Accordingly, applicants respectfully submit that the Pohl et al. reference does not anticipate the present invention because it does not disclose each and every element of the invention as claimed in claims 1, 3 and 7, and this rejection should be withdrawn.

Claims 1-3, 7 and 9-10 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Meyers et al. (Proc. Nat., Acad. Sci., Vol. 72, No. 6, pp. 2193-2196, 1975). Similar to the arguments set forth above, applicants respectfully traverse the rejection and request withdrawal of the Section 102(b) rejection because the cited reference is inapt as Section 102 art, as follows:

The Office Action contends that Meyers et al. discloses deprotecting amines of amino acids and peptides by removing benzyloxycarbonyl (Cbz) with trypsin.

Applicants respectfully submit that, contrary to the Office Action's contention, Meyers et al. does not anticipate the claimed methods in that it fails to disclose a method wherein a non-arginyl containing protecting group and not an arginyl containing protecting group is removed to recover the amine as required in independent claims 1 and 9. Meyers et al.'s method requires the protecting group to contain an arginyl moiety. In contrast, the present invention as hereby claimed in independent claims 1 and 9 describes a method for deprotecting an amine protected with a protecting group that does not contain an arginyl moiety. Rather, the method of the present invention requires in independent claim 1 the removal of the protecting group having the formula $ArC^{*}(R)H\text{-}(CH_2)_n\text{-}O\text{-}C(=O)\text{-}$, wherein R is H or independently the same as Ar, and n is 0 or 1-4, Ar refers to an aromatic or heteroaromatic ring with 5 to 6 ring atoms and wherein the heteroaromatic ring contains one to two heteroatoms selected from O, N or S, which can be substituted with amino, alkanoyloxy, alkoxy, alkyl, alkylamino, allyl, carboxy, cycloalkyl, halo, haloalkyl, hydroxy, hydroxyalkyl or nitro, or up to one group which is (i) Ar^{*} which is independently the same as Ar except that it is not substituted with a further aryl, (ii) Ar^{*}-alkyl- or (iii) $Ar^{*}O$-, a ring atom of Ar adjacent to C^{*} can be substituted with $-CH_2-$, -O-, -NH-, $-S(O)_q-$ or $-P(O)_r-$, to form a bridge to a corresponding position on R when R is Ar, q is 0 or 1-2 and r is 0 or 1-2.

In addition, similar to the arguments set forth above, the Meyers et al. reference is inapt as Section 102 art because it fails to disclose a method of deprotecting a hydroxide protected with a protecting group. Meyers et al.'s method is limited to a method of deprotecting Cbz-arginyl blocked *amines* of amino acids and peptides. In contrast, the present invention as hereby claimed

in independent claim 1 describes a method for deprotecting a moiety that is not limited to Cbz-arginyl blocked *amines* of amino acids and peptides. Rather, the method of the present invention can be used to deprotect a hydroxide protected with a protecting group.

Accordingly, applicants respectfully submit that the Meyers et al. reference does not anticipate the present invention because it does not disclose each and every element of the invention as claimed in claims 1-3, 7 and 9-10, and this rejection should be withdrawn.

The Examiner recognized that these references did not disclose the present invention and attempted to overcome the deficiencies in the teachings of Pohl et al. and Meyers et al. by using them as a basis for the obviousness rejection discussed below.

Rejection Under 35 USC § 103

Claims 1 – 4, 7 - 10 and 15 - 20 stand rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over Pohl et al. and Meyers et al. in view of Williams et al. (US Patent 5,625,030), Wong et al. (US Patent 5,981,267) and Srivastiva et al. (US Patent 5,814,616) and in further view of Robl (US Patent 5,508,272) and Karanewsky et al. (US Patent 5,552,397). Specifically, the Office Action contends that a "person of ordinary skill in the art at the time the invention was made would have been motivated to use just about any suitable enzymatically removable protecting group of the carbonate or urethane type with aromatic groups because such amine and hydroxyl groups are well known in the art as shown by the relied upon and cited art."

Applicants respectfully traverse the foregoing rejection and request reconsideration thereof. It is respectfully submitted that, contrary to the Office Action's assertion on page 6, the Examiner has not established a proper *prima facie* case of obviousness. The U.S.P.T.O. has the initial burden of demonstrating why one skilled in the art would have been motivated to make the proposed modifications needed to arrive at the presently claimed methods. The Office Action contends that (i) Pohl et al. and Meyers et al. show that protecting groups are removable enzymatically from amines; (ii) Williams et al., Wong et al. and Srivastiva et al. establish that the ordinary artisan is reasonably expected to be able to selectively protect and deprotect with such groups on amines and hydroxyls; (iii) selection of one amine compound or another appears to be an arbitrary matter of experimental design choice in as much as the enzyme selectivity is at the protecting group side of the scissile bond; and (v) Robl and Karanewsky et al. show that the specific amines desired are known in the art and desirable to prepare. Based on these contentions,

the Office Action contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to deprotect amines or hydroxyls containing the urethane or carbonate protecting groups enzymatically. However, case law provides that the fact that the claimed invention is within the capabilities of one skilled in the art is not sufficient by itself to establish *prima facie* obviousness under 35 U.S.C. § 103. There must be "some objective suggestion or teaching" in the prior art to combine or modify the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.); *In re Lalu*, 223 USPQ 1257, 1259 (Fed.Cir.1984) ("[i]n determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification."); *In re Jones*, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992) (("Conspicuously missing from this record is any evidence, other than PTO's speculation ... that one of ordinary skill ...would have been motivated to make modifications of the prior art ...necessary to arrive at the claimed [invention]."); and *In re Grabiak*, 226 USPQ 870, 872 (Fed.Cir.1985) ("there must be adequate support in the prior art...in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant.").

At page 5 of the Office Action, the only support for the obviousness rejection is the Office Action's recital that one of ordinary skill would have been motivated to use just about any suitable enzymatically removable protecting group of the carbonate or urethane type with aromatic groups because such amine and hydroxyl groups are well known in the art. No recital of an objective suggestion or teaching in the prior art to make the modifications set forth in the claimed methods of the present invention is provided in the Office Action whatsoever. Accordingly, applicants respectfully submit that the contended obviousness rejection of the claimed compounds is unfounded with respect to the cited references.

Assuming, *arguendo*, that the Office Action has established a proper *prima facie* case of obviousness, applicants respectfully submit that the present application contains evidence of

unexpected results that effectively rebut such. It is respectfully submitted that the methods of the present invention exhibit unexpected results in that stereospecific amines can be produced in enantiomeric excess from racemic mixtures in contrast to what could have been predicted from the prior art. See, in this regard, the data in Table 2 in the present application showing greater than 95% conversion to the L isomer.

Applicants respectfully submit that the presently rejected claims are unobvious and patentable over the prior art. Accordingly, applicants respectfully request the withdrawal of the above-discussed Section 103 rejection.

Objection to Claims

Claims 5 and 6 stand objected to for allegedly depending on a rejected base claim. New claims 21 and 31 serve to make allowable claims 5 and 6 by including all of the limitations of said base claim 1 in them, as suggested by the Office Action, and re-writing them as claims 21 and 31.

Conclusion

In view of the remarks presented above, applicants respectfully submit that the pending claims are in condition for allowance. An early Office Action to that effect is, therefore, earnestly requested.

The Commissioner is hereby authorized to charge any fees that may be required, including any fees under 37 C.F.R. §§1.16 and 1.17, for the filing of this paper to Deposit Account No. 19-3880.

If, in the opinion of the Examiner, a telephone conference with the undersigned would facilitate prosecution of this patent application, the Examiner's call would be welcomed.

Respectfully submitted,

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